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Temporal lobectomy for epilepsy: Recovery of the contralateral hippocampus measured by ^1H MRS

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Abstract

^1H MRS imaging was obtained from 10 patients with mesial temporal lobe epilepsy before and after surgery. After surgery, metabolic recovery in the contralateral hippocampus was detected. Preoperatively, reduced N-acetylaspartate ($p < 0.04$) increased after surgery nonsignificantly to equal control values. Cholines increased after surgery ($p < 0.02$) and creatine–phosphocreatine showed a trend to higher values. The results suggest that the contralateral hippocampus is affected by repeated seizure activity in the ipsilateral hippocampus, rather than presence of bilateral mesial temporal sclerosis.

In mesial temporal lobe epilepsy (mTLE), the epileptogenic hippocampus has reduced concentrations of N-acetylaspartate (NAA). NAA is also frequently reduced in the contralateral hippocampus.^{1,2} Few MRS studies have described metabolic changes following surgery in epilepsy.^{3–5} Two studies found postoperative recovery of NAA in the ipsilateral temporal lobe in patients with TLE who were seizure free after surgery, but no change in patients who were not seizure free.^{4,5} Preoperatively reduced contralateral NAA may be due to 1) bilateral mesial temporal sclerosis; or 2) repeated seizures arising from the ipsilateral hippocampus causing temporary or permanent secondary contralateral changes. However, in neocortical epilepsy (NE), no MRS imaging (MRSI) changes in the hippocampus were found, suggesting that repeated seizures in NE do not lead to hippocampal impairment.⁶ Reductions of NAA are reversible in some diseases.^{4,5,7} If the NAA reduction in the contralateral hippocampus is due to secondary alterations caused by repeated seizures, these changes might be reversible with reduction of seizure frequency. Therefore, we evaluated metabolite changes in the contralateral hippocampus after temporal lobectomy.

Methods

Subjects

Ten patients with unilateral medically refractory mTLE were studied before and 4 to 16 months after surgery (age range: 24 to 49 years, mean age 34.6 ± 9.1 years). The study was approved by the local Committee of Human Research, and informed consent was obtained prior to MRSI

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studies. Anterior-medial temporal lobe resection was performed in all patients. The patients were on the same antiepileptic drugs and dosages before and after surgery. Eight patients were seizure free after temporal lobectomy (Engel class I⁸) and two patients had continued complex partial seizures (class II and class III). The patients were compared to 16 healthy control subjects (age range: 23 to 56 years, mean age: 33.3 ± 7.9 years).

MRSI methods

MRSI studies were performed on a 1.5 T Magnetom VISIONTM (Siemens, Erlangen, Germany). Before and after surgery a water-suppressed 2D-MRSI with point-resolved spectroscopy (PRESS) volume preselection was performed parallel to the long axis of the hippocampus (figure, circular k-space sampling corresponding to 24×24 matrix, field of view: 21 cm, repetition time = 1.8 seconds, echo time = 135 milliseconds), directly followed by an identical MRSI measurement without water suppression.² The anterior border of the hippocampus was used as landmark for positioning of the PRESS-box. In postoperative studies, the PRESS-box was carefully repositioned.

Processing

Spatial zero filling to 32×32 and k-space apodization (effective voxel size ~ 2 mL) was performed. Time domain processing included zero filling to 1,024 data points, Gaussian apodization (2 Hz line-broadening), spectral phasing, and polynomial baseline-correction. Signals of NAA, creatine-phosphocreatine (Cr), choline containing compounds (Ch), and water were curve-fitted. An average of six voxels was selected from both hippocampi. Mean values from those voxels are reported. Voxels were selected at same positions before and after surgery.

Quantitative data were calculated using two methods. The first method used the unsuppressed H₂O-signal as a reference. The corrections required for quantitation have been previously described.² For this method the hippocampal H₂O was assumed to be constant with a content of 80%. Metabolite concentrations in mmol/L were calculated. However, because relaxation times were not determined, the term “apparent concentration” is used for the metabolites. A second method was applied to compare also the H₂O values and the metabolites without referencing to another potentially changed signal in order to exclude the possibility of detecting metabolite changes due to changes in H₂O. This method uses for correction the receiver gain and the coil loading.⁹ Relative metabolite values calculated using method 2 were similar to those for method 1 and therefore are not presented in detail. Only the H₂O values calculated with method 2 are presented in the text and tables 1 and 2.

Statistics

Statistical analyses were done using analysis of variance (ANOVA). The *p* Values were calculated using two-tailed paired and unpaired Student's *t*-tests for comparisons between pre- and postoperative results, and between patients and control subjects. Significance was assumed for probability values of $p < 0.05$ after Bonferroni corrections for multiple comparisons. All data are presented as mean $\pm$ SD.

Results

In the figure, a transverse fast low angle shot image is displayed with an outline indicating the typical PRESS-box location. Pre- and postoperative spectra from the contralateral hippocampus are also shown. Table 1 lists patient characteristics and individual patient results of contralateral hippocampal NAA, Cr, Ch (calculated by quantitation method 1), and H₂O signal (method 2).

Group comparisons using ANOVA showed contralateral hippocampal metabolites (NAA ($p < 0.01$), Cr ($p < 0.03$) and Ch ($p < 10^{-4}$)) were different among pre- and postoperative patients and control subjects. In contrast, little difference was evident for the H₂O signal ($p > 0.05$). Table 2 shows grouped pre- and postoperative metabolite values of the contralateral hippocampus. Prior to surgery, contralateral hippocampal NAA was lower than NAA in control subjects ($p < 0.04$). Following surgery, NAA increased in 7 of 10 patients. Mean NAA rose (nonsignificantly) from 10.1 ± 1.0 to 11.3 ± 1.1 and was no longer significantly different from control subjects. Prior to surgery, Cr and Ch were not different from control subjects. After surgery, Cr increased in 7 of 10 patients. Mean Cr increased nonsignificantly from 9.7 ± 0.9 to 11.0 ± 1.5 , and postoperative Cr showed a trend to higher values than in control subjects. In 9 of 10 patients, Ch also increased following surgery. Mean Ch rose from 2.4 ± 0.3 to 3.1 ± 0.5 ($p < 0.02$), and showed a trend to higher values compared with control subjects. The H₂O signal increased in 8 of 10 patients after surgery, but there was no significant difference between the coil corrected H₂O signal of pre- and postoperative patients and control subjects. Metabolite signals, corrected for receiver gain and coil loading and not referenced to H₂O (quantitation method 2), showed even greater changes after surgery. This demonstrates H₂O signal intensity changes were not responsible for the metabolite changes.

Discussion

Major findings of this study were: 1) following surgical removal of the hippocampus for intractable epilepsy, contralateral hippocampal NAA, which had been significantly reduced prior to surgery, increased nonsignificantly to equal control values; and 2) contralateral hippocampal Cr and Ch, which were not different from control subjects prior to surgery, also increased to above control values after surgery.

The finding of contralateral NAA recovery following surgical removal of the ipsilateral hippocampus is consistent with findings from other studies that demonstrate reversibility of NAA changes.^{4,5,8} Thus, increase of NAA following surgery could reflect recovery of preoperatively impaired contralateral hippocampal neural function. The finding of contralateral hippocampal Ch and Cr increases might reflect diffuse gliosis as a nonspecific consequence of brain surgery.¹⁰ However, the origin of the Cr and Ch increase remains speculative.

The increases in both NAA and in Cr and Ch may reflect a change in cell type and/or metabolism in the contralateral hippocampus after surgery. This finding of a recovery of the contralateral hippocampus after surgery suggests that preoperatively it is affected by repeated seizure activity in the ipsilateral hippocampus, rather than the presence of bilateral mesial temporal sclerosis. The findings suggest that reduced seizure frequency and severity after surgery leads to a rise in contralateral hippocampal NAA.

In NE no metabolite changes were found in both hippocampi, suggesting that repeated seizure activity in NE does not result in hippocampal damage.⁶ However, it is possible that functional connections exist between the hippocampi and may contribute to seizure propagation, whereas seizures arising from the neocortex do not affect hippocampal metabolism.

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Figure.

Demonstration of the typical localization of the MRS imaging measurement superimposed on an oblique transverse image angulated parallel to the long axis of the hippocampus. Spectra from the contralateral hippocampal region before (preop) and after (postop) surgery are shown.

Table 1
Patient characteristics and results of the contralateral hippocampus before and after surgery

Patient no./Age/Sex	Days after surgery	Quantitation method 1						Quantitation method 2	
		NAA		Cr		Ch		H ₂ O	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
1/27/F	117	11.0	12.7	10.7	10.4	2.2	3.4	16.4	13.9
2/24/F	529	11.4	10.6	9.3	10.8	2.1	2.9	11.2	13.6
3/43/M	502	9.7	11.0	8.0	12.0	2.7	4.1	13.8	14.2
4/49/F	341	10.9	10.3	9.4	14.0	2.4	3.0	12.8	14.2
5/28/M	215	9.1	12.4	10.4	12.7	2.3	3.9	13.7	13.8
6/28/M	334	9.7	13.1	8.8	10.5	2.1	3.2	15.4	14.1
7/45/M	250	10.1	11.2	10.7	9.2	1.8	2.7	14.3	14.5
8/26/M	272	8.3	10.7	10.2	9.6	2.6	2.6	14.3	15.3
9/38/M	91	9.8	9.7	8.8	9.5	2.8	3.0	14.0	14.4
10/38/M	320	11.1	11.5	10.3	11.5	2.5	2.7	13.2	15.7

Apparent concentrations for *N*-acetylaspartate (NAA), creatine (Cr), and choline (Ch) are in mmol/L (calculated by quantitation method 1). H₂O denotes (in arbitrary units) the H₂O signal multiplied by the transmitter reference value (calculated by quantitation method 2).

Table 2
Comparison of averaged results of the contralateral hippocampus between patients before and after surgery and control subjects

Metabolite	Quantitation method	Patients	<i>p</i> Value before–after surgery	Control subjects	<i>p</i> Value patients–controls
NAA	1		NS	11.6 ± 1.3	
Before surgery		10.1 ± 1.0			<i>p</i> < 0.04
After surgery		11.3 ± 1.1			NS
Cr	1		NS	9.7 ± 1.3	
Before surgery		9.7 ± 0.9			NS
After surgery		11.0 ± 1.5			NS
Ch	1		<i>p</i> < 0.02	2.6 ± 0.3	
Before surgery		2.4 ± 0.3			NS
After surgery		3.1 ± 0.5			NS
H ₂ O	2		NS	13.4 ± 1.1	
Before surgery		13.9 ± 1.4			NS
After surgery		14.4 ± 0.7			NS

Mean (± SD) pre- and postoperative apparent metabolite concentrations (in mmol/L) in the contralateral hippocampus of patients with mesial temporal lobe epilepsy and in the hippocampus of controls (calculated by quantitation method 1). The H₂O values corrected for coil loading (in arbitrary units, quantitation method 2) are also presented. *p* Values are given for a two-tailed paired (before–after surgery) and unpaired (patients–controls) *t*-test with Bonferroni corrections for multiple comparisons. NAA = *N*-acetylaspartate; Cr = creatine; Ch = choline.